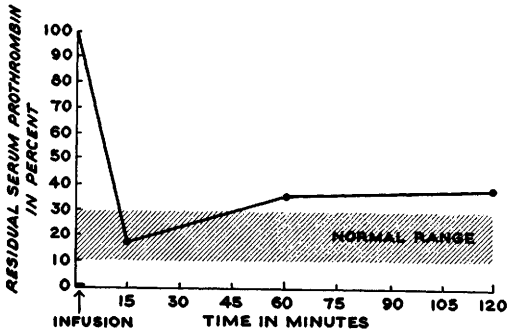

FIG. 3. Effect of rapid intravenous infusion of 20 ml of a 2.5% soybean phosphatide solution on prothrombin utilization in the thrombocytopenic x-irradiated dog. (Serum tested after incubation of blood for one hr at 37°C. Prothrombin determinations by 2-stage method of Ware and Seegers(4).)

prothrombin is shown in Fig. 3.

Summary. Thrombocytopenia, prolonged whole blood clotting time, and markedly impaired clot retraction and prothrombin utilization were induced in dogs by 150 r total body x-irradiation. A marked increase in prothrombin utilization was found after the addition of a soybean phosphatide solution to the blood *in vitro*. A temporary decrease in the clotting time and an increase in prothrombin utilization, without change in the platelet count or clot retraction, was induced by the intravenous administration of 20 to 100 ml of a 2.5% solution of the soybean phosphatide.

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Effect of Glucagon in Stable and Unstable Diabetic Patients. (20367)

W. R. KIRTLEY, S. O. WAIFE, AND F. B. PECK. (Introduced by O. M. Helmer.)
From the Lilly Research Laboratories and Indianapolis General Hospital, Indianapolis, Ind.

A hyperglycemic factor, termed "glucagon" by Murlin *et al.*(1), has been known for 30 years to be present in most commercial insulin preparations. Its isolation, purification, and characterization has been an exceedingly stubborn problem. Recently, the authors have had available for study a preparation of an unusually high degree of purity provided by A. Staub of these Laboratories(2). The material used in this study was of such potency that 0.5 μg of the substance per kg administered intravenously to unfed cats anesthetized with amobarbital produced a rise in the blood sugar of 30 mg per 100 cc above normal within 25 minutes (a "cat unit"). Further animal assays showed it to contain only 0.005 unit of insulin per mg of solid.

During the course of an investigation of the physiological properties of this highly purified hyperglycemic-glycogenolytic factor (glucagon), the authors studied the response of various types of diabetic subjects. In this report only the response of the blood sugar and serum inorganic phosphorus will be discussed. Data relative to pyruvate, lactate, potassium, and certain steroid studies will be presented elsewhere(3).

Technic. An intravenous infusion of diluted glucagon was given both to normal persons and to 8 female diabetic patients. All subjects received 10 μg/kg body weight (10 μg of this material was equivalent to 20 "cat units") in the fasting state; the diabetics had not received insulin on the morning of the test. Since no dose exceeded 1 mg of the test material, no one received more than 0.005 unit of insulin based on animal assay results. Venous blood sugar was determined by the

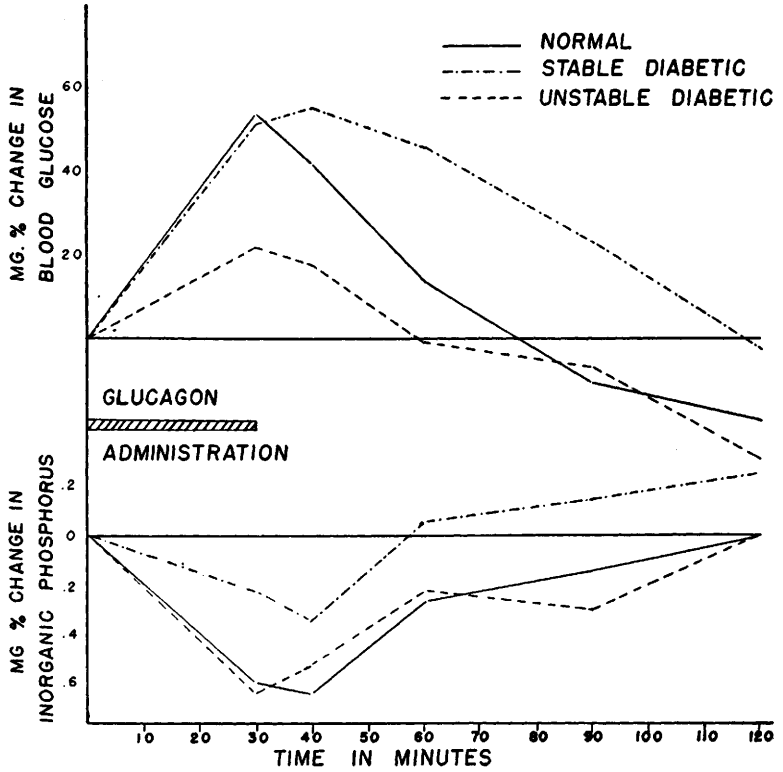

FIG. 1. The effect on blood sugar and inorganic phosphorus of intravenous glucagon in normal subjects and stable and unstable diabetic patients.

Nelson method; inorganic phosphorus, by the Fiske and Subbarrow technic adapted for a photoelectric colorimeter.

Results. The blood sugar levels of the normal presons reached a peak of elevation in about 10 minutes after completion of the infusion and fell to values below the fasting level between 60 and 90 minutes, much as is seen following glucose administration; however, diabetics receiving glucagon in a similar manner showed glycemic responses that could be divided into two patterns (Fig. 1).

In four patients the average blood sugar rose to a level closely approximating that of the normal subjects but fell slowly so that by 90 minutes it still exceeded the initial level, and by 120 minutes, in spite of individual variations, the average was about at the initial level. These patients also showed an impaired fall in serum inorganic phosphorus. The patients in this group seem to have in common the general clinical characteristics of the "stable, adult" type, that is, the middle-aged or elderly, overweight diabetic who is not particularly sensitive to insulin and is not liable to develop ketosis easily.

In 4 other diabetics, however, the blood sugar did not rise as high and fell below the initial value at 60 minutes. (The 60-minute point on the curve shows the differences between the two groups most clearly.) Whereas, at 120 minutes the blood sugar of the first group was at initial levels, it was 29.5 mg per 100 cc below in the second group. It was also noted that the glycemic response bore no relationship to the height of the initial glucose level. Quite in contrast with the other diabetics, these patients had a normal fall in serum phosphorus. Three of the patients in the second group were extremely labile showing spontaneous variations in blood glucose (when determinations were made 4 times daily) of as much as 300 mg per 100 cc or more in a 24-hour period, the insulin and diet remaining unchanged. They are in the category usually designated as being "unstable

and insulin-sensitive."

Discussion. It was assumed that these unstable patients would have an even more abnormal response to endogenous glucose liberated by glucagon than the stable diabetics, in keeping with Bornstein's finding(4), that this type of patient is more likely to be deficient in circulating insulin. It is highly probable that the glycogen content of the liver is reflected in the height of the glucose elevation following glucagon administration. If it is assumed that the stable diabetic has endogenous insulin(4) and the unstable case has none, or very little, and that insulin increases glycogen deposition in the liver, it would appear that the labile diabetic with little or no circulating insulin has low hepatic glycogen stores. Glucagon would then produce a smaller immediate rise in blood sugar in such subjects. Contrariwise, the stable diabetic with his own circulating insulin and greater hepatic glycogen stores would show a normal response to the glycogenolytic factor.

The fall in blood sugar below initial fasting levels after glucose administration is considered by some to be the result of the stimulation of insulin. If this is so, then glucagon stimulated the production or activation of endogenous insulin in the unstable diabetic. This perhaps was mirrored in the normal fall in serum inorganic phosphorus in these patients. According to Forsham and Thorn(5), a fall in serum inorganic phosphorus (following intravenous glucose administration) is "a valid criterion for the peripheral utilization of glucose" and is said to be dependent on the presence of insulin(6-8).

Since the increment in blood sugar following glucagon was relatively small in unstable diabetics, insulin, if stimulated, was not called forth by the additional hyperglycemia, and some other mechanism must have been at work. Other explanations, of course, are possible, but there is no evidence at present to completely explain this phenomenon.

One might speculate that the stable type of diabetic is relatively insulin-insensitive, because he has glucagon to counteract any fall in blood sugar. He has some circulating insulin, but not enough for all metabolic needs, and he has ample liver glycogen. Such a diabetic would be comparable to the partially alloxanized animal. The unstable type of diabetic, on the other hand, may be insulin-sensitive, because he lacks endogenous glucagon needed to modify rapid falls in blood sugar. With little if any available insulin of his own, he may have a relative deficiency of liver glycogen. Such a diabetic would resemble the depancreatized animal.

Summary. A highly purified preparation of glucagon (pancreatic hyperglycemic-glycogenolytic factor, HGF) was administered intravenously to normal and diabetic subjects. Two different types of responses in blood sugar and serum inorganic phosphorus were found between the more common stable and the rarer labile diabetic. The responses seem to fall into patterns compatible with present concepts of the two broad clinical varieties of diabetes mellitus.

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